REMARKS

1. Rejection under 35 U.S.C. 112, First Paragraph

Claims 11 to 13 were rejected under 35 U.S.C. 112, first paragraph, for lacking enablement.

Method of treatment claims 11 to 13 have been amended to help avoid this formal rejection. Claim 12 has been amended to claim different novel and more currently relevant methods of administration, which are particularly adapted to the problem of efficient administration to the site of action, namely the melatonin-specific receptor. Basis for the changes in claim 12 is found on page 3, lines 16 to 17, of the applicants' specification.

The method of treating hyperinsulinemia claimed in claim 11 is basically straightforward and does not require undue experimentation by one of ordinary skill in the art to implement. The method is limited to a single compound, namely melatonin. Thus the only variables involved relate to how much melatonin should be administered and how it should be administered. The specification teaches amount ranges for the melatonin to be administered on page 3 of the specification. The type and amount of auxiliary agent or diluent is not a factor in the method of treatment. The specification on page 3 states that the drugs can be prepared in appropriate dosages between 0.01 and 200 mg of melatonin in the known manner with conventional carriers and diluents.

This latter information is sufficient for one skilled in the art to prepare various tablets, ampoules, adhesive tapes, implants, gels and buccal administration systems with a various dosage between the stated amount limits, namely between 0.01 and 200 mg, of melatonin (page 3 of the specification). Detailed information regarding the manner of making these types of delivery systems is well known to those of ordinary skill in the arts and is not part of the present invention.

It is well established that what is well known in the art is better left out from a patent specification. For example the Federal Circuit Court of Appeals has said:

> "A patent need not teach, and preferably omits, what is well known in the art". ***Hybritech Inc. v. Monoclonal Antibodies, Inc.***, 231 U.S.P.Q. 81(Fed. Cir. 1986).

Detailed methods of preparing tablets, ampoules, adhesive tape, subcutaneous implants and the like are thus better left out of the patent and left to those of ordinary skill in the art because the features of the invention are not directly related to these latter methods.

Although a particularly preferred dosage of melatonin is not disclosed for each type of administration mentioned on page 3 of the specification, one skilled in the art would not have difficulty in preparing e.g. tablets with various amounts of melatonin and administering them in clinical trials or in *in-vivo* model experiments. This experimental program does not put an undue burden on those using the claimed invention.

The test of enablement is whether or not undue experimentation is

required to practice the invention. See M.P.E.P. 2164.01. As a short guide to what is undue experimentation the Federal Circuit found that experimentation was **not** undue when $50,000 and 6 to 12 months of experimentation was required in *United States v. Telectronics, Inc.*, 8 U.S.P.Q. 2nd 1217 (Fed. Cir. 1988). All that is required here is some experimentation regarding a selected method of administration from page 3 and varying dosage amounts, which is routine for pharmaceutical laboratories.

Some factors to be considered in determining whether or not the amount of experimentation required is undue are: breadth of claims, level or ordinary skill in the art; level of predictability, and the amount of experimentation necessary to "fill in the blanks" in the disclosure.

However it is well to remember that compliance with the enablement requirement under 35 U.S.C. 112, 1st paragraph, (in contrast to the statement on page 4 of the Office Action) does **not** turn on whether or not a working example has been provided. See M.P.E.P. 2164.02 and the case law cited therein.

It is true that Bailey, et al, teaches in his general conclusion that administration of melatonin orally in *in vivo* experiments with rats does not lead to significant reduction in plasma insulin levels. However these results involve fewer than seven data points (see Fig. 3 of Bailey, et al). The academic study of Bailey, et al, discloses too few *in vivo* results to make such conclusions regarding the *in vivo* effectiveness of methods of treatment involving administration of melatonin. Designing pharmaceutical compositions requires testing to determine preferred effective dosage levels, which requires many more experiments with different

concentration levels than are disclosed in the Bailey, et al, reference. Perhaps Bailey, et al, should have performed more experiments with *in vivo* model systems with a greater number of melatonin concentrations; the academic study of Bailey, et al, is unconcerned with developing pharmaceutical compositions or methods of treatment. However performing such experiments with varying amounts of melatonin should not be considered undue experimentation, at least within the guidelines of the Federal circuit mentioned above.

One cannot conclude from the very few *in vivo* results of Bailey, et al, that predictability is lacking to such an extent that a correlation cannot be made between the positive *in vitro* experimental results of the applicant that illucidate a mechanism of action based on the melatonin-specific receptor and *possible in vivo* methods of administering melatonin to humans or animals that would understandably lead to reductions in excessive insulin levels.

All that is required for enablement is that a reasonably predictable correlation can be made between any disclosure of positive *in vitro* experimental results and a possible method of treatment of a human or animal. Applicants in vitro experiments in the specification should be considered convincing. Applicants have clearly shown that when pancreatic islets that are stimulated to produce excessive amounts of insulin are also exposed to melatonin in the amounts disclosed in the applicants' specification and included in the above claims the insulin production will be significantly reduced (see figs. 1 and 2 of applicants' specification).

The level of ordinary skill in the art is now considerably higher than in

many arts and the same is true of predictability. Pancreatic cells can now be transplanted or removed from the body and treated outside the body (as a search of the Internet shows). Subcutaneous implants are routinely used to deliver drugs, e.g. cancer treating drugs, to a site in the body where they must act. In many cases the drugs would not be effective if administered orally because they are metabolized -- that is the reason for the subcutaneous implant to deliver the drugs to the required site.

For example, applicants disclose a subcutaneous implant to deliver the melatonin at about line 17 of page 3 of the applicants' specification. An adhesive tape or patch for delivery of melatonin, which is applied to the body in the vicinity of the pancreas, is also disclosed. These latter systems would clearly avoid metabolization of melatonin in the digestive system after oral administration.

Thus applicants contend that their specification contains sufficient information and that there is a sufficient correlation between the *in vitro* experiments in the specification and the method claimed in claim 11 so that one skilled in the art could practice the method of claim 11 *without undue experimentation.* More experimentation with many more concentrations of melatonin would not constitute undue experimentation for one skilled in the art.

As long as one transports the melatonin to the G protein-coupled membrane-bound receptors in tact, excessive insulin production should be suppressed or reduced to a significant extent as shown by the experiments of figs. 1 and 2 of the applicants. Clearly some of the methods of administration mentioned on page 3 are preferable to others, but undue experimentation is not

necessary for one skilled in the art to practice the method of claim 11.

For the foregoing reasons withdrawal of the rejection of amended claims 11 to 13 under 35 U.S.C. 112, first paragraph, for lack of enablement is respectfully requested.

Furthermore it is respectfully submitted that new method claims 14 to 17 should not be rejected for lack of enablement under 35 U.S.C. 112, first paragraph.

New method claim 14 claims a method of reducing insulin release from pancreatic islets by administering a pharmacologically effective amount of melatonin to the pancreatic islets. The basis for this method is the disclosure of the experimental work that shows that administration of melatonin to pancreatic islets *in vitro* reduces the amount of insulin secreted by the pancreatic islets. These experiments are described under the heading "Functional Demonstration ...Islets" in the specification on pages 3 to 4. They were performed with adequate controls and produced significant statistical results shown in figures 1 and 2. The effective amount of melatonin of dependent claim 16 is disclosed on line 7 of page 3 of the English language specification of the above-identified application. The particular amounts of melatonin used in the experiments are disclosed in the last two lines of page 3 of the specification.

The specification on pages 3 and 4 teaches all the critical features that are necessary to practice the claimed method of claim 14. Details that have been omitted such as methods of obtaining and handling pancreatic islets are well

known in the art. No special procedures in this latter regard are necessary. It is well established that what is well known in the art is better left out from a patent specification. For example the Federal Circuit Court of Appeals has said:

> "A patent need not teach, and preferably omits, what is well known in the art". ***Hybritech Inc. v. Monoclonal Antibodies, Inc.***, 231 U.S.P.Q. 81(Fed. Cir. 1986).

Methods of handling and obtaining pancreatic islets are well known in the art and thus do not need to be disclosed in the applicants' patent specification.

The critical variables in the experiments that demonstrate reducing the stimulated insulin generation from the pancreatic islets are the compositions of the solutions that are administered, i.e. the amounts of the melatonin and other ingredients of the solutions administered to the pancreatic islets. Figure 2 teaches the amount of the stimulant forskolin administered and page 3, last two lines, teach the melatonin concentration in the administered solution.

Undue experimentation is not required to enable one skilled in the art to perform this method.

For the foregoing reasons it is respectfully submitted that none of the new method claims 14 to 17 should be rejected under 35 U.S.C. 112, first paragraph, for lack of enablement.

2. Anticipation Rejection based on Lewy, et al

Claims 11 to 13 were rejected under 35 U.S.C. 102 (e) as anticipated by Lewy, et al.

The Office Action admits that no prior art discloses treatment of hyperinsulinemia by administering melatonin to a person suffering from that condition.

The rejection of claim 11 was based on an inherency argument (M.P.E.P. 2112.02). The Lewy U.S. Patent teaches a method of administering melatonin to treat circadian rhythm disturbances, such as insomnia, jet lag and winter depression or blues. The argument in the Office Action is that there is an overlap between populations suffering from insomnia and excess insulin production by the pancreatic islets and that the method of Lewy, et al, in its normal operation, is sufficient for treatment of hyperinsulinemia.

On the contrary M.P.E.P. 2112.02 clearly states that a new use of an old compound is clearly patentable (under "PROCESS OF USE" claims).

The argument in the Office Action is based on a factual relationship, namely that the population suffering from insomnia, i.e. due to interference with normal circadian rhythm by e.g. jet lag, would include significant numbers of those suffering from hyperinsulinemia, i.e. those in which their pancreatic islets generate too much or excessive amounts of insulin.

The citation of a prior art reference showing a connection between those suffering from hyperinsulinemia and sleep disorders, such as insomnia, is

respectfully requested.

Also clarification is requested: Is the argument in the Office Action that there is a known causal or other connection between hyperinsulinemia and sleep disorders or is the argument based on the chance occurrence that *some* individual suffering from sleep disorders like insomnia are also suffering from hyperinsulinemia?

If the argument is based on a known connection between sleep disorders and hyperinsulinemia, then a prior art reference that discloses this connection and proves that it exists should be cited to support the argument or it should be withdrawn because Lewy, et al, do not mention pancreatic islets, the pancreas or disorders of these tissues. Lewy, et al, do not mention anything regarding insulin levels in the body or the amount of insulin produced by pancreatic islets or problems due to excessive amounts of insulin produced by the pancreas.

If the argument is based on the chance occurrence of a few individuals suffering from sleep disorders who are also suffering from hyperinsulinemia, then it should be pointed out that during the administration of melatonin to treat the sleep disorders in the normal operation of the method of the Lewy, et al, reference, the method does not necessarily result in treatment of hyperinsulinemia or excessive levels of insulin produced by the pancreatic islets because the person suffering from the sleep disorders might not be suffering from hyperinsulinemia. In other words, when melatonin is administered to an individual suffering from a sleep disorder, hyperinsulinemia is not necessarily being treated, because the individual does not usually have an excessive amount

of insulin in his system. Furthermore individuals with diabetes also suffer from sleep disorders treated with melatonin.

In order for a claimed method to be inherently disclosed in a prior art reference, the claimed method must always be performed when the method disclosed in the prior art reference is performed. It is well established that the test of inherency is not satisfied by what a reference "may" teach. "Inherency may not be established by probabilities or possibilities." See ***Continental Can Co. U.S.A. v. Monsanto Co.***, 20 U.S.P.Q. 2nd 1746, 1749 (Fed. Cir. 1991); ***SSG Thomson Microeletronics, Inc. v. International Rectifier Corp.***, 32 U.S. P.Q. 2nd 1496, 1503 (Fed. Cir. unpublished).

In other words, the performance of the claimed method of claim 11 must always occur when the method disclosed in the reference is performed. That is not the case with the claims of the present application because when melatonin is administered to individuals suffering from sleep disorders the claimed method is not always performed (because the individuals do not always have an excessive amount of insulin in their systems).

The claimed method of claim 11 is clearly a new use for the compound administered in the method of Lewy, et al.

For the foregoing reasons withdrawal of the rejection of claims 11 to 13 under 35 U.S.C. 102 (e) by Lewy, et al.

Regarding new method of reducing insulin release claims 14 to 17 Lewy, et al, is unconcerned with direct treatment of pancreatic islets or insulin release from pancreatic islets.

Lewy, et al, teach none of the features of new method claim 14.

It is respectfully submitted that claims 14 to 17 should not be rejected under 35 U.S.C. 102 (e) based on Lewy, et al.

Should the Examiner require or consider it advisable that the specification, claims and/or drawing be further amended or corrected in formal respects to put this case in condition for final allowance, then it is requested that such amendments or corrections be carried out by Examiner's Amendment and the case passed to issue. Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing the case to allowance, he or she is invited to telephone the undersigned at 1-631-549 4700.

In view of the foregoing, favorable allowance is respectfully solicited.

Respectfully submitted,

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